REMARKS

Applicants again would like to thank the Examiner for conducting the interview on April 1, 2009. As set out in the Interview Summary, during the interview proposed claim amendments, Saslawski et al. (WO99/33448) and the advantages of the invention were discussed.

Claims 1, 2, 5, 8-11, 19, 25-26 and 31 are pending in this application.
Claim 31 is new.
Claims 1, 11, 19, and 25-26 have been amended.
Claims 3, 4, 6, 7, 12-18, 20-24 and 27-30 are cancelled.

The amendments to claims 1, 11, 19, 25 and 26 will be discussed below.
Support for new claim 31 is found on page 8 of the specification.

It is also understood by those of skill in the art that release sustaining materials as referred to on page 6 of the specification are release controlling materials and support for the said release sustaining materials as release controlling materials is provided in pages 8 and 9 of the specification. A release sustaining material is a material that will control the release of a compound. This is also supported by original claims 1 and 11.

According to page 2 of the Office Action, claims 1, 2, 4, 5, 8-11, 15, 19 and 25-30 are allegedly rejected under 35 U.S.C. 103(a) as being unpatentable over Saslawski et al (WO99/33448) in view of Gibson et al (US6426340) based on US Provisional Application 60/018202. This rejection is respectfully traversed.

In order to expedite prosecution of this application that has been pending since 2003, Claim 1 has been amended to include release controlling materials that were included in claim 4 as included in the previously filed response. Claim 4 has now been cancelled. The phrase cellulose and cellulose derivatives has been replaced by the cellulose derivatives included in the paragraph bridging pages 9 and 10 of the specification.

This amendment is being made without prejudice to applicants' rights to file any number of continuation and/or divisional applications for any subject matter disclosed in this application and not presently claimed including compositions. Applicants do not intend to forego any

subject matter disclosed in this application and this amendment shall not be considered limiting in terms of prosecution history estoppel.

As amended, claim 1 now defines a once-a-day controlled release tablet composition consisting of single unit fast release layer comprising nimesulide and single unit extended release layer comprising nimesulide and one or more release controlling materials in an effective amount to control the release of nimesulide from said composition and wherein the release controlling materials are selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides. Support for the release controlling materials can be found in the specification on page 9 and in examples 1, 2, 3, 4, 5, 8, 9, 10, and 11. The amount of the release controlling material(s) present in the extended release layer is effective to control the release of nimesulide from said layer.

The release controlling materials of the composition do not act as binders or disintegrants.

Claims 11, 19 and 25 as amended herein, includes the same release controlling materials as in claim 1. The same explanation as above for claim 1 is incorporated herein.

The release controlling materials as included in the claims do not include non-biodegradable, inert, polymeric matrix as described in Saslawski et al.

In claim 26, as amended herein, hydroxypropyl methylcellulose has been described as the release controlling material, this distinguishes from the hydroxypropyl methylcellulose or other cellulose derivatives used in Saslawski et al which are used as either disintegrants (See page 9, lines 21-24) or as binder (See page 12, lines 3-7) and not as release rate controlling material. Support for the amendment to claim 26 is based on the use of hydroxypropyl methyl cellulose as a release controlling material, the disclosure in the last paragraph on page 9 and Example 10.

The claimed composition that includes these rate controlling materials is not obvious in view of the disclosure of Saslawski et al.

Saslawski et al. teach a multilayer tablet that can be made up of only two layers i.e. a first layer (immediate or fast release layer) and second layer (prolonged release layer containing a nonbiodegradable, inert porous polymeric matrix). See page 2, lines 19-30. Saslawski et al teach that the second layer constitutes an inert matrix that does not become eroded and does not swell in an aqueous medium (See page 3, line 33-35) and that the essential constituents of the second prolonged-release layer are polymeric materials which confer on it its inert and nonbiodegradable character. The polymers or copolymers are insoluble in water, not forming a gel and are discharged intact by the body (See page 12, lines 10-15).

The polymeric matrix of the second layer in Saslawski et al. are in particular polyvinyl chlorides, vinyl acetate copolymers and copolymers of (meth) acrylic acids, which are further specifically described and are commercially available as Eudragit® polymers (See page 12 and 13).

Saslawski et al. specifically teaches use of such a nonbiodegradable inert polymeric matrix in the second layer, which are conferred by polymers of methacrylic acid derivatives or copolymers of (meth)acrylic acids (Eudragit® series), to ensure release of the active ingredient independently of the influence of the body (and in particular pH variations) (See page 19, lines 1-25). All examples illustrated in Saslawski et al. utilize Eudragit series of polymers (methacrylic acid derivatives) to achieve prolonged release of active ingredient. It is noted that Saslawski et al neither teach nor suggest the use of biodegradable material in second layer (extended release layer) for prolonging the action of NSAIDs, more preferably nimesulide.

Saslawski et al. teach away from Claim 1, as amended herein. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant" *In re Gurley* 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious).

One of ordinary skill in the art following the teachings of Saslawski et al. would be taught first outer layer allowing immediate release of a first active substance (page 2, line 3-26) and a second layer containing a nonbiodegradable, inert porous polymeric matrix (page 2, lines 27-30) and that these polymers or copolymers [are] insoluble in water (but not forming a gel either upon immersion in an aqueous medium) (page 22, lines 8-15). One of ordinary skill in the art would find no motivation to provide a formulation as defined in independent claims 1, 11 and 25 and dependent claim 19 of nimesulide with single unit fast release layer comprising nimesulide and single unit extended release layer containing release controlling materials selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides in an amount effective to control the release of nimesulide from the extended release layer.

Submitted with this response are a number of references that describe that these release controlling materials are biodegradable and/or gel or swell and erode in the presence of water. As described above, these release controlling materials differ from those disclosed in Saslawski et al. The following information supports that the release controlling materials used in the claimed invention are biodegradable unlike those used in Saslawski that are not biodegradable.

1) Cellulose and cellulose derivatives: R. Chandra, Renu Rustgi, Biodegradable Polymers, Prog. Poly. Sci. Vol. 23, 1273-1335, 1998, Section 2.1 –Second paragraph and Section 2.1.2

2) Gelatin: R. Chandra, Renu Rustgi, Biodegradable Polymers, Prog. Poly. Sci. Vol. 23, 1273-1335, 1998, Section 2.2.1

3) Polyalkylene polyols (polyethylene glycols): Bernhard et al. Water Research 42 (2008), 4791-4801, whole article and conclusion. Also attached is a printout from Wikipedia that describes that polyethylene glycol and polyethylene oxide are the same.

4) Gum Arabic: Ramakrishnan et al., Biosource Technology 98 (2007):368-372. See abstract.

5) Xanthan gum: S. Rosalam et al., Enzyme and Microbial Technology 39 (2006) 197-207. See page 199 Section 2-Fifth paragraph.

The Examiner states on page 3 of the Office Action that Saslawski et al. allows for the inclusion of NSAID compounds which would suggest the inclusion of Nimesulide (or the sulfonanilide compound class). It is emphasized that neither nimesulide nor any other sulfonanilide derivative has been disclosed by Saslawski et al. Although Saslawski et al. on page 5, lines 6-20, describes certain types of NSAIDs, those that include aryl propionic acid derivatives, aryl acetic acid derivatives, aryl carboxylic acid derivatives, anthranilic derivatives, and indole derivatives it does not "teach" NSAIDs that are sulfonanilide derivatives and does not teach or suggest nimesulide. (*See Merck & Co., Inc., V. Biocraft Laboratories*, United States Court of Appeals, Federal Circuit – 874 F.2d 804).

Therefore, the Examiner has not established a *prima facie* case of obviousness.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. 82 USPQ2d at 1396.

Claim 1, as amended herein, now specifically recites the release controlling materials of the extended release layer to be selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides most of which are hydrophilic in nature and which hydrate and swell in presence of water or body fluids,

thus the release controlling materials are NOT nonbiodegradable, inert porous polymeric matrix like the copolymers of (meth)acrylic acid derivatives as required by Saslawski et al

This clearly distinguishes the present invention from the teachings of Saslawski et al. which neither teaches nor suggests a once-a-day controlled release tablet composition of a single unit fast release layer comprising nimesulide and a single unit extended release layer comprising nimesulide and one or more release controlling materials selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides.

Although it is disclosed on page 9, line 10 and page 12 that the prolonged release layer of Saslawski et al. can comprise hydroxypropyl methylcellulose and sodium lauryl sulfate, the hydroxypropyl methylcellulose or other cellulose derivatives (like carboxymethyl cellulose) and carbomers used in Saslawski et al, are being used as either disintegrating agent (See page 9; lines 21-24) or as binder (See page 12; lines 3-7) but not as a release controlling material, which is how it is being used in the compositions of nimesulide of this invention. During the interview held on April 1, 2009; Examiner indicated that the amount of release controlling material in the range 5% to 65% w/w on page 5 of the specification and claim 2 of present invention overlaps with the range of 0 to 15% by weight of disintegrating agent disclosed on page 9, lines 19-20 of the Saslawski, et al. and considered that the release controlling material may act as a disintegrating agent in the said range. Applicant herein would like to explain by including the definitions of binder and disintegrant that these terms differ in meaning from the term release controlling material as used by applicant in amended claim 1, 11, 15, 19, 25 and 26.

Rudnic et al. Chapter 92 Oral Solid Dosage Forms, Remington: The Science and Practice of Pharmacy; Vol 11, 19th Edition, Mack Publishing Company, Pennsylvania 1995. Pages No. 1615-1620, defines the terms binder and disintegrants.

According to Rudnic (Page no 1617; first paragraph under binder); binders are the agents which impart cohesive quality to the powdered materials. They generally impart cohesiveness to the tablet formulation which insures the tablet remaining intact after compression as well as improving the free-flowing property by the formulation of granules of desired hardness and size. Material commonly used as binder includes starch, gelatin, and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include acacia, sodium alginate, and extract of Irish Moss, Panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Vegum and larch arabogalactan. Other agents that can be used as binders are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

One of ordinary skill in the art very well understands the role and functions of binders. Binders are generally used in an amount only to provide sufficient binding to the matrix material and are used as additives in the formulation (these do not contribute as release controlling materials).

Rudnic further provides the definition of disintegrator at page no 1619; according to Rudnic; disintegrator is a substance, or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, cellulose, alginates, gums and cross-linked polymer. However, while present composition of nimesulide comprises gums (either synthetic or natural), gelatin, alginates, carbomers, polyalkylene polyols, polycarbophils, polyethylene oxides and cellulose derivative, these are used as a rate controlling material not as binders and disintegrants.

The present composition of nimesulide comprises an effective amount of release controlling material which controls the release of drug over a period of time. The effective amount of said release controlling material as claimed in claim 1 can be in the range between 0.1 % w/w to 99% w/w, (or 5% w/w to 65% w/w as in claim 2) of the total composition provided that the said release controlling materials significantly contribute to control the release of drug over a period of time. With respect to Saslawski et al; the amount of disintegrating agent is in the range between 0 to 15% and acts as a disintegrating agent regardless of the amount of said disintegrating agent. Saslawski et al do not disclose that the use of 'such disintegrating agents

in a particular amount or ratio may act as a release controlling material. While in present invention applicant uses release controlling material in an effective amount to control the release of nimesulide from said composition.

Thus Saslawski et al does not teach use of cellulose and cellulose derivatives, and carbomers as release controlling materials as has been described in the specification and claims 1, 11, 19, 25 and 26, as amended herein. Thus mere disclosure of hydroxypropyl methylcellulose and sodium lauryl sulphate in Saslawski et al does not teach or suggest their use as release controlling materials.

Therefore, it is clear that the claimed invention is not obvious Saslawski et al.

In KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 167 L. ED.. 2nd 705 (2007), the Supreme Court held that the obviousness analysis of *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S.Ct. 684, 15L. Ed. 2nd 545 (1966), controls an obviousness inquiry. The Graham obviousness factors include "the scope and content of the prior art" and the "differences between the prior art and the claims". KSR, 127 S.Ct. at 1734 (quoting Graham, 383 U.S. at 17-18). Prima facie obviousness may be overcome by a showing of commercial success.

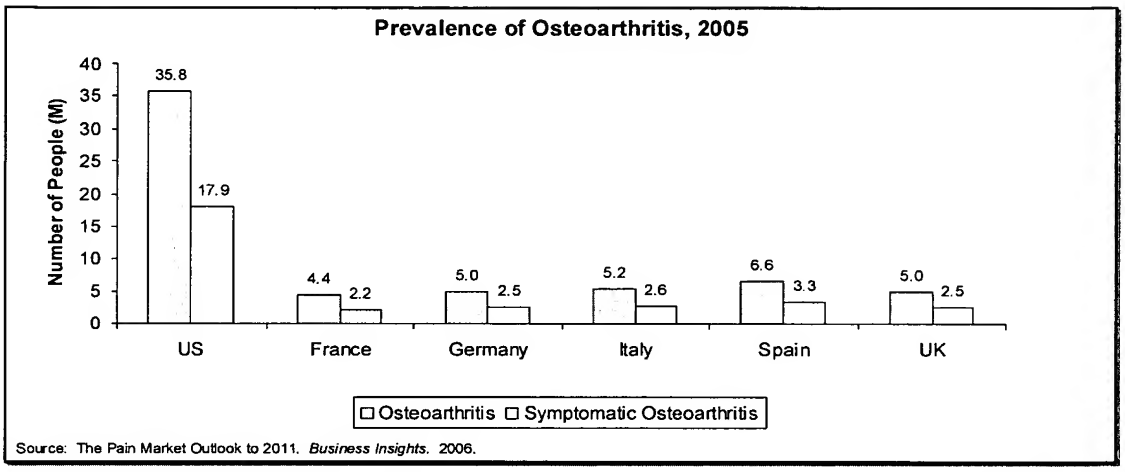
Although, as stated above, it is applicants' position that no prima facie showing of obviousness has been made, as further evidence that the claimed invention is not obvious over Saslawski et al., being filed with this response is the declaration of Dr. Rajesh Jain, one of the inventors of the claimed subject matter. Dr. Jain describes experiments that were conducted that establish the advantages of the claimed invention compared to an immediate release composition of nimesulide and a composition comprising Diclofenac. Dr. Jain also describes the commercial success of the claimed invention.

The information about commercial success is repeated below.

It is known that osteoarthritis (OA) is a progressive bone and joint disorder that can lead to severe joint pain and decreased patient mobility. It is estimated that within the US and the EU the prevalence of osteoarthritis is approximately 62 million people. About half of these patients (31 million) experiences pain related to OA (Symptomatic OA). The prevalence of

people with symptomatic OA is estimated at 17.9 million (6.1% of the total population) in the US and 13.1 million (4.3%) for the top five largest European market[i].

Fig 1:



The prevalence of OA rises with age. In fact – in the US, the over-65 population accounts for more than half of all OA cases. The prevalence of OA rises from 8.4% in patients aged 35-44 to 41.4% for patients above the age of 65.[ii] The anticipated growth in the elderly population is anticipated to result in an increased prevalence of OA in the major global markets. The US is expected to have an additional 9 million more people aged 65 and older in 2020 than in 2006.

Osteoarthritis Treatment Paradigm

First-line treatment options for OA (acetaminophen and lifestyle recommendations) are successful to a limited extent. Patients typically shift to either traditional NSAIDs or selective COX-2 inhibitors as second-line therapy. Some patients may progress further and require treatment for flare-ups (corticosteroids, hyaluronic acid) or invasive surgery.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely available for decades. Due to their well-established efficacy and dosing profile, they remain commonly used agents for mild-to-moderate OA. However, they may cause serious GI side effects with long-term use. Long-term use of any of the traditional NSAIDs, may damage the mucous layer of the stomach, resulting in general stomach discomfort or, more seriously bleeding and ulcer formation.

Selective COX-2 inhibitors are a subset of NSAIDs that specifically inhibit the COX-2 enzyme. The intent of this specificity is to reduce GI side effects commonly associated with

the traditional NSAIDs. However, the COX-2 class has been associated with a higher incidence of cardiovascular side effects.

Physicians make their treatment choice based on four primary factors since comparative studies have found no clear efficacy differences:

- Dosing and Frequency
- Gastrointestinal Risks
- Cardiovascular Risks
- Renal Risks

Physicians must balance the different risks based on individual patient circumstances – but none of the current therapies provide the combination of simplified dosing with minimal GI, cardiovascular and renal risks.[iii]

Nimesulide Extended Release tablet is positioned to meet the identified unmet needs with current therapeutics for the treatment of OA. Panacea Biotec's brand Willgo®, based on the present invention (bilayered, controlled release Nimesulide tablets), sold in India, has been proven to be a highly effective product for the management of chronic OA pain and inflammation offering the advantage of once a day dosing with favorable GI tolerability and good safety in Cardio Vascular and Renal parameters. Panacea's product was introduced in India as a new drug delivery product supported by promising clinical trial results. The product was able to address a significant unmet medical need which resulted in consistently growing sales. As an example the IMS-ORG audited data for the last three years is presented below:

Table 1: Sales of Willgo® Tablet (Extended Release Nimesulide) and Nimulid® Tablet (Immediate Release Nimesulide) in India

PBL BRANDS	Apr-Dec 06	MAT DEC 07	MAT DEC 08	Apr-Dec 06	MAT DEC 07	MAT DEC 08
	ABS Value	ABS Value	ABS Value	ABS Units	ABS Units	ABS Units
WILLGO TABS	23,555,210	34,804,568	42,599,763	594,829	863,637	995,150
NIMULID TABS	94,715,001	106,154,891	102,530,488	4,079,327	4,313,504	4,168,075

ABS Value means Absolute Amount in Rupees
ABS Units means Absolute Number of Strips of Each Brand (Each Strip contains 10 Tablets)
MAT Means Moving Annual Total
TABS means Tablets

The Table 1 indicates the sales growth of Willgo® Tablet (Extended Release Tablet) and Nimulid® Tablet (Immediate Release Tablet) in absolute value and units for the period i.e. Apr 2006-Dec 2006, Jan 2007-Dec 2007 and Jan 2008 to Dec 2008.

Conclusion: It has been concluded from the above table that the sales growth of Willgo® (Extended Release Nimesulide) is increasing year by year. Percentage growth Sales of Willgo® has increased by 80.8% in last two years from Dec 2006 to Dec 2008. While percentage sales growth of Nimulid® Tablet (Immediate Release Nimesulide) has increased only by 8.25 in last two years from Dec 2006 to Dec 2008 and decreased by 3.4 in last one year from Dec 2007 to Dec 2008.

i. The Pain Market Outlook to 2011. Business Insights. 2006.
ii. Singh, G et al. Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis: Data from the Third National Health and Nutrition Examination Survey. The American Journal of Managed Care. Vol. 8, No. 15, Sup.
iii. Chou R, Helfand M, Peterson K, et al. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Comparative Effectiveness Review No. 4. Prepared by the Oregon Evidence-based Practice Center. Prepared for the Agency for Healthcare Research and Quality. September 2006. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed on September 12, 2007.

When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of all the evidence, including the evidence submitted by the examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). Therefore, the Examiner must consider the evidence in Dr. Jain's declaration and the evidence of commercial success.

In regard to Gibson, this reference has no relevance whatsoever to the present claims. It does not bridge the gap with any mention of nimesulide or bilayered once-a-day controlled release tablet as claimed herein; it only mentions use of silicon dioxide in immediate and controlled release formulation, which the Examiner would agree is already well-established in the art.

There is no suggestion or motivation in the combination of the cited references to combine the references to develop a once-a-day controlled release composition of nimesulide as claimed in this application and no reasonable expectation of success to achieve its success in the market place.

Neither Saslawski et al nor Gibson et al., singly or in combination, teach or suggest a once-a-day controlled release composition of nimesulide consisting of single unit fast release layer comprising nimesulide and single unit extended release layer comprising nimesulide and one or more release controlling materials and wherein the release controlling materials are specified from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides.

In light of the scope and content of the prior art and in light of the differences between the prior art and the claims, applicant respectfully submits that claim 1, as amended herein, is patentable over the combined teachings of Saslawski et al and Gibson et al. Claims 2, 5, 8, 9, 10 (previously amended), 19 (currently amended) and 31 (new Claim) depend directly or indirectly, on claim 1, as amended herein. Under 35 U.S.C. 112, fourth paragraph, "a claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers". "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious". MPEP 2143.03; *In refine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants respectfully submit that all of the claims as herein, are patentable over the combined teachings of Saslawski et al and Gibson et al.

Therefore, it is respectfully requested that the rejection be withdrawn.

It is submitted that the present application is in condition for allowance and favorable consideration is respectfully requested. If any issues remain, please contact the undersigned.

Respectfully submitted,

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